BMJ Open

The Clinical Efficacy of Transcutaneous Electrical Nerve Stimulation (TENS) for Acute and Chronic Pain: A Protocol for a Meta-Analysis of Randomized Controlled Trials (RCTs)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029999
Article Type:	Protocol
Date Submitted by the Author:	21-Feb-2019
Complete List of Authors:	Johnson, Mark; Leeds Beckett University Faculty of Health and Social Sciences, Centre for Pain Research Jones, Gareth; Leeds Beckett University, School of Clinical and Applied Sciences Paley, Carole; Leeds Beckett University, School of Clinical and Applied Sciences; Airedale NHS Foundation Trust, Research & Development Wittkopf, Priscilla; Leeds Beckett University - City Campus, School of Clinical and Applied Sciences
Keywords:	Transcutaneous electrical nerve stimulation, Pain, Systematic review, Meta-analysis

Title

The Clinical Efficacy of Transcutaneous Electrical Nerve Stimulation (TENS) for Acute and Chronic Pain: A Protocol for a Meta-Analysis of Randomized Controlled Trials (RCTs)

Authors

Mark I. Johnson, PhD[1]

Gareth Jones, PhD[1]

Carole Paley, PhD[1,2]

Priscilla Wittkopf, PhD[1]

Affiliations

1. Centre for Pain Research, Clinical and Applied Sciences, Leeds Beckett University, Leeds, LS1 3HE, U.K.

2. Research & Development Dept. Airedale NHS Foundation Trust, Steeton, Keighley BD20 6TD

Address for correspondence

Professor Mark I. Johnson

Telephone: (UK) 0113 2832600, e-mail: m.johnson@leedsbeckett.ac.uk

Word count: 3879

ABSTRACT

Introduction: The aim of this systematic review with meta-analysis is to determine the clinical efficacy of TENS for acute and chronic pain in adults.

Methods and analysis: We intend to search databases from inception to the present day to identify all systematic reviews and meta-analyses, including Cochrane reviews, on the use of TENS in adults for any type of pain including acute pain, chronic pain, and cancer-related pain. We will identify all RCTs included in each systematic review and use these RCTs in the analysis. Two reviewers will independently undertake RCT selection, data extraction, and risk of bias assessment. Primary outcomes will be: (i) participant-reported pain relief of 30% or greater expressed as frequency data (dichotomous data); and (ii) participant-reported change in pain intensity expressed as mean data (continuous data). We will conduct meta-analyses using risk ratio for dichotomous data, and mean difference or standardised mean difference for continuous data to determine clinical efficacy versus placebo TENS, no treatment or waiting list control, standard of care (including exercise), and other treatments. Subgroup analyses will include different pain conditions (e.g. acute versus chronic), TENS intensity, during versus after TENS, TENS as a sole treatment versus TENS in combination with other treatments, and TENS administered as a single dose versus repetitive dose.

Ethics and dissemination: This systematic review will not use data from individual participants, and the results will be disseminated in a peer-reviewed publication and presented at a conference.

Keywords: Transcutaneous electrical nerve stimulation, Pain, Systematic review, meta-analysis

Article Summary

Strengths and limitations of this study

- The majority of systematic reviews of the efficacy of TENS for specific medical conditions published to date have been inconclusive due to insufficient data. The strength of this systematic review is that the broad inclusion criteria will seek to ascertain statistical power.
- A limitation of this systematic review is that the different forms of TENS administration and quality of methodologies in the included studies may cause heterogeneity.

INTRODUCTION

The worldwide prevalence of chronic pain in the general adult population is between 15-30 per cent.[1-4] Pain is financially expensive in terms of medical consultations, treatments and time lost from work, and socially expensive in terms of suffering and impaired quality of life.[5 ,6] Gaskin and Richard [5] estimated that annual costs related to health care and loss of worker productivity in the United States was between $560 and $635 billion dollars. This was greater than heart disease ($309 billion), cancer ($243 billion), and diabetes ($188 billion). In Europe, Breivik, et al. [7] estimated the national healthcare and socioeconomic costs of chronic pain to be 3-10% of gross domestic product.

Approximately 40 per cent of people living with chronic pain report inadequate pain management and over 60 per cent report that medication dose not adequately control pain.[8] Desirable pain-management strategies adopt a biopsychosocial approach using pharmacological and non-pharmacological interventions tailored to the individual. The goal of treatment is to relieve pain and improve physiological functioning associated with activities of daily living, role functioning associated with jobs and hobbies, and emotional, cognitive and social functioning to improve quality of life. Early pain management is critical to reduce the likelihood of acute pain evolving into chronic pain. Transcutaneous electrical nerve stimulation (TENS) has been used across the world for the management of acute and chronic pain irrespective of cause [9]

Description of the intervention

TENS is the delivery of pulsed electrical currents across the intact surface of the skin to stimulate peripheral nerves, principally for pain relief.[9] TENS may be self-administered by the patient, ideally following instruction from a healthcare practitioner using a portable, battery-powered TENS device to produce electrical currents that are delivered to the body using self-adhesive electrodes attached to the surface of the skin. TENS is available without prescription, is inexpensive and has a good safety profile compared with medication.[9] Contraindications include patients who also have cardiac pacemakers and implantable cardioverter defibrillators. Precautions include pregnancy, epilepsy, active malignancy, deep-vein thrombosis, and frail or damaged skin.[10 ,11] Two techniques are commonly used: conventional TENS administered to produce a strong non-painful TENS sensation at the site of pain and acupuncture-like TENS to produce strong non-painful pulsate sensations with muscle twitching.[9] Evidence suggests that currents with pulse amplitudes (mA) that generate a strong, non-painful TENS sensation are critical for response and therefore pulse amplitude should be titrated during treatment to maintain this intensity level.[12-14] There has

been a long-standing debate about the efficacy of TENS. Some clinical guidelines recommend TENS as an adjunct to core treatment whereas others do not.[10 ,15]

How the intervention might work

In 1965, Melzack and Wall [16] proposed that TENS could stimulate the low-threshold cutaneous afferents to inhibit onward transmission of nociceptive information in the central nervous system and thus, alleviate pain (i.e. segmental modulation;[17 ,18]). In addition, TENS could stimulate small diameter muscle afferents to activate descending pain inhibitory pathways [19-21] or block afferent activity in peripheral neurons, creating a 'busy-line' effect.[22]

Previous Reviews

There is a plethora of systematic reviews on TENS for specific conditions and most are inconclusive (for review see [15 ,23]) An overview of Cochrane reviews provides tentative evidence that TENS reduces pain intensity when administered as a stand-alone treatment for acute pain in adults.[24] A meta-analysis found superiority of TENS over placebo for reducing postoperative analgesic consumption when administered using a strong, subnoxious intensity and adequate frequency.[12] A Cochrane review to assess the effects of TENS on pain in labour found limited evidence of effect but concluded women should have the choice of using it during childbirth.[25]

In 2008, a Cochrane review on TENS for chronic pain was inconclusive [26] although it has now been withdrawn. An overview of Cochrane reviews on TENS for chronic pain included nine reviews and 51 RCTs conducted a descriptive analysis with no attempt to pool data.[27] It was not possible to conclude weather TENS was beneficial or harmful.[27] Most Cochrane reviews on specific chronic pain conditions are inconclusive (e.g. osteoarthritis of the knee [28], neuropathic pain [29], chronic low back pain [30], cancer pain [31], and phantom pain and stump pain.[32] Non-Cochrane meta-analyses have found superiority of TENS over placebo for chronic musculoskeletal pain [33], and osteoarthritis of the knee.[34]

Systematic reviews and meta-analyses are hindered by methodological weaknesses. Bennett, et al. [35] found that inadequate method of randomisation, small sample sizes, and issues associated with the implementation of a sham (placebo) control such as allocation concealment and blinding contributed to an overestimation of effects in TENS studies. The design of authentic placebo controls is a challenge. Credible sham TENS devices have been used that are identical in appearance to real TENS devices and deliver no current or deliver stimulation at the start of treatment and fade to zero

current output over a brief period of time (e.g. within 45 seconds).[36] It is not possible to blind participants to TENS sensation. Uncertainty about allocation to active and inactive TENS can be achieved by informing participants that some types of electrical stimulation devices do not produce sensation during stimulation (i.e. microcurrent therapy). Blinding can be monitored by asking participants whether they believed that '...the device was functioning properly?'.[37] Aspects of fidelity that may contribute to underestimation of the effects of TENS include inadequacy of TENS technique; inadequate dosing; and the effect of concurrent analgesia in placebo groups.[35]

Why it is important to do this review

Debate about the clinical efficacy of TENS for the relief of pain in adults has been ongoing since TENS was introduced in the early 1970s. The majority of systematic reviews published to date have been inconclusive, despite a vast number of published RCTs. This has resulted in contradictory recommendations from clinical guideline panels. For example, the National Institute of Health Care Excellence (NICE) recommend that TENS should be offered as an adjunct to core treatment for osteoarthritis [38] but not for non-specific chronic low back pain.[39]

Previous systematic reviews tend to focus on pain associated with specific medical conditions. This markedly reduces sample sizes of pooled data and the statistical power of the meta-analysis. In general, the findings of systematic reviews of the efficacy of TENS for specific medical conditions are inconclusive due to insufficient data. Methodological factors influencing estimates of efficacy include analyses used to measure treatment outcome, trial duration, withdrawals, and statistical imputation following withdrawal. According to the Cochrane collaboration, trial arms with fewer than 200 participants in RCTs or fewer than 500 participants in meta-analyses are at a high risk of bias seriously undermining confidence in findings.[40] To date, only two meta-analyses on TENS have come close to this threshold of acceptability and both found superiority over placebo (for acute post-operative pain [12] and chronic musculoskeletal pain[33]). Pooling data on pain intensity from RCTs irrespective of diagnostic condition would markedly improve the statistical power associated with meta-analyses of TENS. The recent overview of Cochrane reviews published by the Cochrane collaboration made no attempt to pool data and was inconclusive.[27]

The mechanism of action of TENS primarily involves neuromodulation of central nociceptive transmission irrespective of medical diagnosis. Therefore, TENS is used for symptomatic relief of pain rather than treatment (cure) of pathology. There has been no convincing evidence that TENS outcome is affected by the nature of pathology, the type of pain, or medical diagnoses.[9 ,41]

Moreover, Loeser has suggested that the dichotomy of pain into acute and chronic should be abolished because pathophysiological processes do not dichotomize at specific time points.[42] Thus, it seems logical to undertake a meta-analysis of the clinical efficacy of TENS irrespective of medical condition. This would increase statistical power and confidence in findings. Concerns over an increase in clinical heterogeneity associated with combining different clinical conditions can be offset by conducting sub-group analyses of specific medical conditions if sufficient data is available.

Aim

The aim of this systematic review with meta-analysis is to determine the clinical efficacy of TENS for acute and chronic pain in adults. The review protocol has been adapted from a Cochrane review on TENS for fibromyalgia previously published by the investigators.[43]

METHODS

Criteria for considering studies for this review

Types of studies

We plan to include randomised controlled trials (RCTs) of TENS treatment for acute or chronic pain. We will exclude studies that are non-randomised, case reports and clinical observations. We plan to include parallel group and crossover trial designs. We plan to include single treatment interventions without follow-up. However, we will give credence to RCTs that deliver at least two weeks of treatment and have a duration of at least eight weeks. We require full journal publication of a full trial report. We will not include, online clinical trial results, summaries of otherwise unpublished clinical trials, abstracts or letters.

Types of participants

We will include RCTs of adult participants aged 18 years or above with any type of clinical pain.

Types of TENS interventions

We will include all RCTs that administer TENS as non-invasive electrical stimulation of the skin with the intention of exciting peripheral nerves to alleviate pain using a standard TENS device.[9]

Non-invasive

We will only include RCTs that administered TENS across the intact surface of the skin using surface electrodes. We will exclude invasive nerve stimulation techniques such as percutaneous electrical nerve stimulation and electro-acupuncture.

Type of TENS Device

We will only include RCTs that administer TENS using a standard TENS device,[9] regardless of the device manufacturer, that delivers biphasic or monophasic pulsed electrical currents. We will exclude RCTs that administer 'TENS-like' currents that are not typical output specifications of a standard TENS device.[9] This includes neuromuscular electrical stimulation (NMES) devices, interferential current devices, and microcurrent devices.[9] We will exclude TENS delivered using single probe electrodes (i.e. TENS pens) or using matrix electrodes and electrode arrays.

TENS Technique

We will include RCTs irrespective of the term used to describe the type of TENS technique (e.g. conventional TENS, Acupuncture-Like TENS, high-frequency-low-intensity, low frequency-high intensity, etc.). We will exclude RCTs that do not use pulsed electrical currents. We will only include RCTs that administer TENS on areas of the body that were sensate at (a) the site of pain or (b) over nerve bundles proximal (or near) to the site of pain. We will include TENS delivered at acupuncture points only if the point was lying over nerve bundles proximal (or near) to the site of pain. We will include all RCTs irrespective of the current amplitude of TENS and/or participant-reported TENS intensity. We consider participant-reported strong but comfortable TENS sensations as optimal and will conduct a subgroup analysis to compare TENS at intensities described as 'strong' (optimal) versus those described as 'mild', 'faint', or 'barely perceptible' (sub-optimal). We will include RCTs that deliver TENS at intensities reported to generate muscle twitches providing TENS is administered using a standard TENS device with the primary goal to alleviate pain. We will only include RCTs that deliver TENS pulse frequencies less than 250 pulses per second and pulse durations less than 1 millisecond. We will include any type of pulse pattern.

Dosage and Regimen

We will include RCTs that administer TENS for any duration or regularity of treatment. We will include TENS that is administered by a therapist and/or self-administered by study participants.

Evaluation of TENS Treatment Effects

We will include TENS administered as a sole treatment or in combination with usual care and/or other treatments. We will exclude RCTs where it was not possible to isolate the effects of TENS from other treatments. We will include RCTs that evaluate TENS versus:

- placebo TENS (e.g. sham (no current) TENS device);

- no treatment or waiting list control;
- standard of care (including exercise); and
- another treatment, both pharmacological and non-pharmacological.

Criteria and Credibility of Placebo TENS

The credibility and blinding of placebo TENS is an issue in TENS studies as it is not possible to blind participants to TENS sensation, although it is possible to generate uncertainty about allocation to active and inactive TENS.[37] We define a sham TENS device as a device similar in appearance to the real TENS device used in the study but where the current output has been modified so that there is no electrical current, or a barely perceptible electrical current and/or electrical current that ceases within one minute.[14 ,36] We will give credence to RCTs that attempt to assess the credibility of placebo TENS.

Types of outcome measures

We will include RCTs that measure pain using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We will include measures of pain at rest and pain on movement. We plan to extract outcome measurement data before, during, and after the intervention, where data is available.

Primary outcomes

- Participant-reported pain relief of 30% or greater expressed as frequency data (dichotomous data).
- Participant-reported change in pain intensity expressed as mean data (continuous data)

Secondary outcomes

- Participant-reported pain relief of 50% or greater.
- Any participant-reported pain-related outcomes other than pain intensity.
- Any participant-reported change in health-related quality of life, including activities of daily living and fatigue, using any validated tool (e.g. SF-36, SF-6, EuroQol).
- Patient Global Impression of Change scale.
- Treatment Satisfaction.
- Participant-experienced adverse events expressed as frequency (dichotomous data) and/or severity.

Pain responses do not follow a normal (Gaussian) distribution.[44 ,45] We have used the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) to define reductions in pain. For dichotomous data we define moderate as 30%>50% reduction over baseline, and substantial as ≥50% reduction over baseline, and for continuous data as no important change (< 15%), minimally important change (15>30%), moderately important change (30%>50%) and substantially important change (≥ 50%).[46] We will capture data for adverse effects of any type or severity as descriptions from participants and number of withdrawals. Serious adverse events are defined as untoward medical occurrence or effect resulting in death, threat to life, hospitalisation, significant disability or incapacity, congenital anomaly or birth defect.

Search methods for identification of studies

The systematic review process will be guided by the Cochrane Collaboration of Systematic Reviews [40] and the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.[47] The purpose of the search is to provide comprehensive coverage of a wide variety of pain types within acute, chronic and palliative settings that have met the quality criteria for inclusion within a previously published systematic review. The first step is to identify all systematic reviews and meta-analyses, including Cochrane reviews, on the use of TENS in adults for any type of pain including acute pain, chronic pain, and cancer-related pain. The second step is to identify all RCTs (completed and awaiting classification) included in each systematic review. The third step will be to remove duplicates and screen them against our eligibility criteria.

Electronic searches

We will search the following electronic databases using a combination of controlled vocabulary, i.e. medical subject headings (MeSH) and free-text terms to identify published systematic reviews from inception to the date of the search.

- Cochrane Library (CENTRAL);
- MEDLINE (via PubMed);
- Embase (via OVID);
- CINAHL (via EBSCO);
- PsycINFO (via EBSCO);
- LILACS (via Birme);
- PEDRO;
- Web of Science;
- AMED (via OVID);

- SPORTDiscus (via EBSCO).

We will tailor searches to the individual databases by adapting the MEDLINE search strategy for the other databases listed (see MEDLINE search strategy in Supplementary material). There will be no language restrictions and we will identify all relevant RCTs irrespective of language and will translate articles where required.

Data collection and analysis

Selection of studies

Two review authors will independently screen records to identify systematic reviews. We will eliminate records that clearly do not satisfy the inclusion criteria, and will obtain full copies of the eligible systematic reviews. Two review authors will identify RCTs on TENS for inclusion by reading the full report of each systematic review. A list of RCTs included in each systematic review will be generated and duplicates removed. Disagreements at any stage of the process will be resolved by consensus using a third review author as arbiter. We will not anonymise records of systematic reviews or RCTs in any way before assessment. We will create a PRISMA flow chart.[40 ,47]

Data extraction and management

Two review authors will extract data from included RCTs independently using a standard form and will check for agreement before entry into a software. Disagreement will be resolved by consensus with a third author acting as arbiter. We will include information about study design, study participants, sample size, and interventions used. We will use this data to populate a 'Characteristics of included RCTs' table (see list of data to be extracted in supplementary material).

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[40] Risk of bias assessment consists of assessment of selection bias, attrition bias, blinding and sample size (see criteria in supplementary material).

Measures of treatment effect

Where available and appropriate we will present quantitative and intention-to-treat (ITT) data.

Primary outcomes

Participant-reported pain relief of 30% or greater expressed as frequency data (dichotomous data).
For dichotomous data (responder analyses) we intend to calculate risk ratio (RR) and risk difference (RD) with 95% confidence intervals (CI). We intend to calculate the number needed to treat to benefit (NNTB) as an absolute measure of treatment effect where possible.

Participant-reported change in pain intensity expressed as mean data (continuous data)
We intend to calculate mean difference (MD) with 95% CI for continuous data collected on identical scales. We intend to calculate standardised mean difference (SMD) with 95% CI for continuous data collected on different scales.

Secondary outcomes

Dichotomous and continuous data will be analysed using the same procedures described for primary outcomes. For health-related quality of life data, we intend to consider a clinical difference greater than 10% of the scale employed to be minimally important.[48]

Clinically important effect

Pain outcomes tend to have a U-shaped distribution with some patients experiencing substantial reductions in pain and others experiencing minimal or no improvement.[49] Thus, data expressed as averages may be misleading as a small average between-group effect size may represent a proportion of participants that actually responded very well to the intervention.[50] We do not know whether outcomes are bi-modally distributed in trials of TENS but we expect most RCTs in this review to present effect sizes as the average between intervention groups. There is little consensus or evidence regarding what the threshold should be for a clinically important difference in pain intensity based on the between-group difference during or after the intervention. IMMPACT thresholds estimate the degree of within-person change from baseline to determine clinically important effects. The OMERACT 12 group states that the proportion of patients achieving one or more thresholds of improvement from baseline pain (e.g. > 10%, ≥ 20%, ≥ 30%, ≥ 50%) should be reported in addition to mean change.[51] We intend to use a threshold of 10 mm on a 0 to 100 mm VAS for minimally important outcome for pain when analysing average between-group change. We will interpret these findings with caution as it remains possible that estimates that fall close to this point may reflect a treatment that benefits an appreciable number of patients

Unit of analysis issues

We will include cross-over designs but intend only to enter the first period data into the meta-analysis. If this was not reported we will note this and not include the data. If data is reported appropriately then we intend to include the data using the generic inverse variance feature.

Dealing with missing data

An intention-to-treat (ITT) analysis will be used when the ITT population were randomised, received at least one dose of TENS, and provided at least one post-baseline outcome measurement. Missing participants will be assigned zero improvement wherever possible.

Assessment of heterogeneity

We will deal with clinical heterogeneity by combining RCTs that examine similar conditions and conducting sub-group analyses. We will undertake separate analyses of TENS compared with different controls (placebo, waiting list, standard of care). We will examine heterogeneity using visual inspection of forest plots, L'Abbé Plots [52], the I^2 statistic and the Chi^2 test, if appropriate.[53] We will classify heterogeneity as not important (0% to 40%), moderate (30% to 60%), substantial (50% to 90%) and considerable (75% to 100%). We will use subgroup analyses to explore significant heterogeneity. Pre-planned comparisons are described in the section Subgroup analysis and investigation of heterogeneity.

Assessment of reporting biases

Publication bias will be assessed using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean a NNTB of 10; Moore [54]). The influence of small study samples will be assessed using the risk of bias criterion "study size". We plan to visually inspect funnel plots to explore the likelihood of reporting biases if there are at least 10 RCTs in a meta-analysis and if RCTs differed in sample size. We will use Egger's test to detect small study bias for RCTs using continuous outcomes.[40]

Data synthesis

We will pool data using Review Manager [55] and will undertake meta-analyses of outcome data using a fixed effect or random-effects model depending on outcome measures and heterogeneity (i.e. I^2 statistics). We will group data according to outcome and measurement time points (i) during stimulation or immediately after stimulation at each treatment session, or both; and (ii) post-intervention follow-up at less than two weeks post-intervention (short-term), two to seven weeks post-intervention (mid-term), and eight weeks or more post-intervention (long-term).

We plan to undertake a narrative synthesis if data is inadequate to support statistical pooling.

Quality of the Evidence

We consider single RCTs too imprecise, unless the sample size is greater than 400 participants for continuous data and greater than 300 events for dichotomous data. We will present the outcome of the 'Risk of bias' assessments in the reporting. We consider pooled data to be imprecise unless the sample size for a treatment arm is greater than 500 participants. We will present pooled effects for outcomes with GRADE judgements in 'Summary of findings' tables. Two review authors will independently rate the quality of outcomes using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system (GRADEpro GDT 2015, see supplementary material for GRADE criteria).

Subgroup analysis and investigation of heterogeneity

We plan to undertake subgroup analyses for acute versus chronic pain and for specific painful conditions. We also plan to conduct subgroup analyses investigating the possible impact of TENS technique on analgesic efficacy as follows:

- Optimal intensity described as > 'strong' versus sub-optimal intensity described as 'barely perceptible', 'faint', or 'mild';
- Conventional TENS (no visible muscle contraction) versus AL-TENS (visible phasic muscle contractions);
- Assessment during TENS versus after TENS;
- TENS administered as a sole treatment versus TENS administered in combination with other treatments; and
- TENS administered as a single dose versus repetitive dose.

Post subgroup analysis we contemplate conducting a network meta-analysis contingent on meeting transitivity assumption.

Sensitivity analysis

We plan to analyse the effect of excluding RCTs with high risk of bias and the effect of using a random-effects versus a fixed-effect model if sufficient data are available.

Ethics and dissemination

This systematic review will not use data from individual participants to protect privacy, and the results will be disseminated in a peer-reviewed publication and presented at a scientific conference.

Funding

The review is funded by an Investigator Sponsored Study grant from GlaxoSmithKline. No external assistance was provided for the design, delivery or writing of this review.

Competing interests

Mark I. Johnson's institution has received research and consultancy funding for work that he has undertaken for GlaxoSmithKline.

Acknowledgements

None

Accessing research materials

Underlying materials related to this protocol and subsequent review can be accessed by contacting Professor Mark I. Johnson.

Author contributions

MIJ conceived the study.

MIJ and PGW created the first draft of the protocol which was then revised by GJ and CP.

The search strategy was developed by PGW.

All authors approved the publication of the protocol.

REFERENCES

1 Elzahaf RA, Tashani OA, Unsworth BA, et al. The prevalence of chronic pain with an analysis of countries with a Human Development Index less than 0.9: a systematic review without meta-analysis. *Current medical research and opinion* 2012;28(7):1221-9. doi: 10.1185/03007995.2012.703132 [published Online First: 2012/06/16]

2 Jackson T, Thomas S, Stabile V, et al. A Systematic Review and Meta-Analysis of the Global Burden of Chronic Pain Without Clear Etiology in Low- and Middle-Income Countries: Trends in Heterogeneous Data and a Proposal for New Assessment Methods. *Anesth Analg* 2016;123(3):739-48. doi: 10.1213/ANE.0000000000001389

3 Fayaz A, Croft P, Langford RM, et al. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open* 2016;6(6):e010364. doi: 10.1136/bmjopen-2015-010364

4 Macfarlane GJ. The epidemiology of chronic pain. *Pain* 2016;157(10):2158-9. doi: 10.1097/j.pain.0000000000000676

5 Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012;13(8):715-24. doi: 10.1016/j.jpain.2012.03.009 [published Online First: 2012/05/23]

6 Goldberg D, McGee S. Pain as a global public health priority. *BMC Public Health* 2011;11(1):770.

7 Breivik H, Eisenberg E, O'Brien T. The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care. *BMC Public Health* 2013;13:1229-29. doi: 10.1186/1471-2458-13-1229

8 Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006;10(4):287-333. doi: S1090-3801(05)00086-8 [pii] 10.1016/j.ejpain.2005.06.009 [published Online First: 2005/08/13]
9 Johnson M. Transcutaneous electrical nerve stimulation (TENS). Research to support clinical practice. Oxford, UK: Oxford University Press 2014.
10 Johnson MI, Bjordal JM. Transcutaneous electrical nerve stimulation for the management of painful conditions: focus on neuropathic pain. *Expert review of neurotherapeutics* 2011;11(5):735-53. doi: 10.1586/ern.11.48 [published Online First: 2011/05/05]
11 Houghton P, Nussbaum E, Hoens A. Electrophysical agents. Contraindications and Precautions: An Evidence-Based Approach to Clinical Decision Making in Physical Therapy. *Physiotherapy Canada* 2010;62(5):5-80.
12 Bjordal JM, Johnson MI, Ljunggreen AE. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. *Eur J Pain* 2003;7(2):181-8.
13 Moran F, Leonard T, Hawthorne S, et al. Hypoalgesia in response to transcutaneous electrical nerve stimulation (TENS) depends on stimulation intensity. *J Pain* 2011;12(8):929-35. doi: S1526-5900(11)00444-5 [pii] 10.1016/j.jpain.2011.02.352 [published Online First: 2011/04/13]
14 Sluka KA, Bjordal JM, Marchand S, et al. What Makes Transcutaneous Electrical Nerve Stimulation Work? Making Sense of the Mixed Results in the Clinical Literature. *Physical therapy* 2013;May 2. [Epub ahead of print] doi: ptj.20120281 [pii] 10.2522/ptj.20120281 [published Online First: 2013/05/04]
15 Johnson MI, Jones G. Transcutaneous electrical nerve stimulation: current status of evidence. *Pain Manag* 2017;7(1):1-4. doi: 10.2217/pmt-2016-0030
16 Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150(3699):971-9. [published Online First: 1965/11/19]
17 Garrison DW, Foreman RD. Effects of transcutaneous electrical nerve stimulation (TENS) on spontaneous and noxiously evoked dorsal horn cell activity in cats with transected spinal cords. *Neuroscience Letters* 1996;216(2):125-8.
18 Ma YT, Sluka KA. Reduction in inflammation-induced sensitization of dorsal horn neurons by transcutaneous electrical nerve stimulation in anesthetized rats. *Experimental Brain Research* 2001;137(1):94-102.
19 Desantana JM, da Silva LF, de Resende MA, et al. Transcutaneous electrical nerve stimulation at both high and low frequencies activates ventrolateral periaqueductal grey to decrease mechanical hyperalgesia in arthritic rats. *Neuroscience* 2009
20 Francis RP, Johnson MI. The characteristics of acupuncture-like transcutaneous electrical nerve stimulation (acupuncture-like TENS): a literature review. *Acupuncture and Electro-Therapeutics Research* 2011;36(3-4):231-58. [published Online First: 2011/01/01]
21 Kalra A, Urban MO, Sluka KA. Blockade of opioid receptors in rostral ventral medulla prevents antihyperalgesia produced by transcutaneous electrical nerve stimulation (TENS). *The Journal of pharmacology and experimental therapeutics* 2001;298(1):257-63.
22 Nardone A, Schieppati M. Influences of transcutaneous electrical stimulation of cutaneous and mixed nerves on subcortical and cortical somatosensory evoked potentials. *Electroencephalogr Clin Neurophysiol* 1989;74(1):24-35.
23 Johnson MI. Transcutaneous electrical nerve stimulation (TENS) as an adjunct for pain management in perioperative settings: a critical review. *Expert review of neurotherapeutics* 2017;17(10):1013-27. doi: 10.1080/14737175.2017.1364158
24 Johnson MI, Paley CA, Howe TE, et al. Transcutaneous electrical nerve stimulation for acute pain. *Cochrane Database Syst Rev* 2015;6:CD006142. doi: 10.1002/14651858.CD006142.pub3 [published Online First: 2015/06/16]
25 Dowswell T, Bedwell C, Lavender T, et al. Transcutaneous electrical nerve stimulation (TENS) for pain relief in labour. *Cochrane Database Syst Rev* 2009(2):CD007214.

26 Nnoaham KE, Kumbang J. Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Database Syst Rev* 2008(3):CD003222.
27 Gibson W, Wand BM, Meads C, et al. Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2019(2) doi: 10.1002/14651858.CD011890.pub2
28 Rutjes AW, Nuesch E, Sterchi R, et al. Transcutaneous electrostimulation for osteoarthritis of the knee. *Cochrane Database Syst Rev* 2009(4):CD002823.
29 Gibson W, Wand BM, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults. *Cochrane Database Syst Rev* 2017;9:CD011976. doi: 10.1002/14651858.CD011976.pub2
30 Khadilkar A, Odebiyi DO, Brosseau L, et al. Transcutaneous electrical nerve stimulation (TENS) versus placebo for chronic low-back pain. *Cochrane Database Syst Rev* 2008(4):CD003008.
31 Hurlow A, Bennett MI, Robb KA, et al. Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. *Cochrane Database Syst Rev* 2012;3:CD006276. doi: 10.1002/14651858.CD006276.pub3 [published Online First: 2012/03/16]
32 Johnson MI, Mulvey MR, Bagnall AM. Transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain following amputation in adults. *Cochrane Database Syst Rev* 2015;8:CD007264. doi: 10.1002/14651858.CD007264.pub3 [published Online First: 2015/08/19]
33 Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: a meta-analysis of randomized controlled trials. *Pain* 2007;130(1-2):157-65.
34 Bjordal JM, Johnson MI, Lopes-Martins RA, et al. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials. *BMC musculoskeletal disorders* 2007;8:51.
35 Bennett MI, Hughes N, Johnson MI. Methodological quality in randomised controlled trials of transcutaneous electric nerve stimulation for pain: low fidelity may explain negative findings. *Pain* 2011;152(6):1226-32. doi: S0304-3959(10)00751-7 [pii] 10.1016/j.pain.2010.12.009 [published Online First: 2011/03/26]
36 Rakel B, Cooper N, Adams HJ, et al. A new transient sham TENS device allows for investigator blinding while delivering a true placebo treatment. *J Pain* 2010;11(3):230-8. doi: 10.1016/j.jpain.2009.07.007
37 Deyo RA, Walsh NE, Schoenfeld LS, et al. Can trials of physical treatments be blinded? The example of transcutaneous electrical nerve stimulation for chronic pain. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists* 1990;69(1):6-10.
38 National Institute for Health and Care Excellence. Osteoarthritis: care and management. NICE guidelines [CG177] London, 2014:1-37.
39 National Institute for Health and Care Excellence. Low back pain and sciatica in over 16s: assessment and management. Clinical guideline [NG59]: National Institute for Health and Care Excellence (NICE), 2016:1-18.
40 Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0 [Updated March 2011], 2011.
41 Johnson MI, Ashton CH, Thompson JW. An in-depth study of long-term users of transcutaneous electrical nerve stimulation (TENS). Implications for clinical use of TENS. *Pain* 1991;44(3):221-9.
42 Loeser JD. A new way of thinking about pain. *Pain Manag* 2018 doi: 10.2217/pmt-2018-0061
43 Johnson MI, Claydon LS, Herbison GP, et al. Transcutaneous electrical nerve stimulation (TENS) for fibromyalgia in adults. *Cochrane Database Syst Rev* 2017;10:CD012172. doi: 10.1002/14651858.CD012172.pub2
44 Moore RA, Straube S, Aldington D. Pain measures and cut-offs - 'no worse than mild pain' as a simple, universal outcome. *Anaesthesia* 2013;68(4):400-12. doi: 10.1111/anae.12148 [published Online First: 2013/01/26]

45 O'Brien EM, Staud RM, Hassinger AD, et al. Patient-centered perspective on treatment outcomes in chronic pain. *Pain Med* 2010;11(1):6-15. doi: 10.1111/j.1526-4637.2009.00685.x [published Online First: 2009/09/08]
46 Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9(2):105-21.
47 Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews* 2015;4(1):1.
48 Furlan AD, Malmivaara A, Chou R, et al. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015;40(21):1660-73. doi: 10.1097/brs.0000000000001061 [published Online First: 2015/07/25]
49 Moore RA, Moore OA, Derry S, et al. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. *Annals of the Rheumatic Diseases* 2010;69(2):374-9. doi: 10.1136/ard.2009.107805 ard.2009.107805 [pii] [published Online First: 2009/04/15]
50 Moore RA, Derry S, Wiffen PJ. Challenges in design and interpretation of chronic pain trials. *British journal of anaesthesia* 2013;111(1):38-45. doi: 10.1093/bja/aet126
51 Busse JW, Bartlett SJ, Dougados M, et al. Optimal Strategies for Reporting Pain in Clinical Trials and Systematic Reviews: Recommendations from an OMERACT 12 Workshop. *J Rheumatol* 2015 doi: 10.3899/jrheum.141440
52 L'ABBÉ KA, Detsky AS, O'rourke K. Meta-analysis in clinical research. *Annals of internal medicine* 1987;107(2):224-33.
53 Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557
54 Moore RAB, J.; Derry, S.; McQuay, H.J. Managing potential publication bias. In: McQuay HJ KE, Moore RA, ed. Systematic Reviews in Pain Research: Methodology Refined. Seattle: IASP Press 2008:15-25.
55 Review Manager (RevMan) [program]. 5.3 version. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Supplementary material

MEDLINE Search Strategy:

1. EXP Transcutaneous Electric Nerve Stimulation/

2 TENS.ti,ab

3 TNS.ti,ab

4 ENS.ti,ab

5 transcutaneous electric* nerve stimulation.ti,ab.

6 transcutaneous nerve stimulation.ti,ab

7 electric* nerve stimulation.ti,ab

8 electrostimulation therap*.ti,ab

9 electro-stimulation therap*.ti,ab.

10 electric* nerve therap*.ti,ab

11 electroanalgesi*.ti,ab

12 transcutaneous electric* stimulation.ti,ab.

13 TES.ti,ab

14 or/1-13

15 Pain

16 Systematic review. Pt.

17 Meta-analysis.pt.

18 16 OR 17

19 14 AND 15 AND 18

Data extraction

- Study Design
  - Cross-over, parallel-group,
  - Setting
  - Study duration
  - Methods of sequence generation and allocation concealment, blinding, intention-to-treat or per protocol analysis
- Study Participants
  - Age, gender
  - Pain diagnosis, duration of pain and symptoms
- Sample size
  - Active and comparator groups
- Interventions used
  - TENS
    - Type of TENS device (e.g. standard or 'TENS-like')
    - Electrode placement
    - Electrical characteristics of TENS (pulse frequency, waveform, amplitude/intensity, duration)
    - Dosage (treatment time and frequency)
    - Setting (where TENS was applied and by whom)
    - Adverse effects
  - Comparison group(s)
    - Type
    - Method of delivery (e.g. if placebo TENS then details of electrode placement, characteristics of placebo TENS (pulse frequency, waveform, amplitude/intensity, duration)
    - Dosage (treatment time and frequency)
    - Setting (where it was applied and by whom)
    - Adverse effects
  - Concomitant treatments
    - Pharmacological and non-pharmacological
  - Outcomes
    - Type
    - Time points used including follow-up

- Withdrawals
- Adverse and serious adverse effects
- Other

Sponsorship, country of origin, conflict of interest statements.

Assessment of risk of bias in included studies

- Random allocation sequence generation (checking for possible selection bias)
    - Low risk of bias - any truly random process, e.g. random number table; computer random number generator
    - Unclear risk of bias - method used to generate sequence not clearly stated
    - We will exclude studies using a non-random process such as odd or even date of birth; hospital or clinic record number
- Allocation concealment (checking for possible selection bias)
    - Low risk of bias - e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes
    - Unclear risk of bias - method not clearly stated
    - High risk of bias - studies that do not conceal allocation (e.g. open list)
- Blinding of outcome assessment (checking for possible detection bias)
    - Blinding of participants
        - Low risk of bias - participants blinded to allocated intervention and unlikely that blinding broken
        - Unclear risk of bias - insufficient information to permit judgement of low/high risk of bias
        - High risk of bias - participants not blinded to allocated intervention OR participants blinded to allocated intervention but it was likely that blinding may have been broken
    - Blinding of care provider
        - Low risk of bias - care provider blinded to allocated intervention and unlikely that blinding broken
        - Unclear risk of bias - insufficient information to permit judgement of low/high risk of bias
        - High risk of bias - care provider not blinded to allocated intervention and the two interventions clearly identifiable to the care provider as experimental and control OR care provider blinded to allocated intervention but likely that blinding was broken
    - Blinding of assessor
        - Low risk of bias - outcome assessor (including 'participants' with respect to self-report outcomes) blinded to participants' allocated intervention and unlikely that blinding broken

- Unclear risk of bias - insufficient information to permit judgement of low/high risk of bias
- High risk of bias - outcome assessor (including 'participants' with respect to self-report outcomes) un-blinded to participants' allocated intervention OR outcome assessor blinded to allocated intervention but likely that blinding was broken

- Incomplete outcome data (drop-outs)
  - Low risk of bias < 20% drop-out and appears to be random with numbers per group provided along with reasons for drop-out
  - Unclear risk of bias < 20% and unclear if random with numbers per group and reasons for drop-out not described
  - High risk of bias ≥ 20% drop-out
- Incomplete outcome data (protocol violations)
  - Low risk of bias - if participants were analysed in the group to which they were originally assigned
  - Unclear risk of bias - where insufficient information is provided to determine if analysis was per protocol or intention-to-treat
  - High risk of bias - where per protocol analysis was used, where available data were not analysed or participants' data were included in the group to which they were not originally assigned
- Selective reporting
  - Low risk of bias - study protocol was available and all pre-specified outcomes were reported or study protocol was not available but all expected outcomes were reported
  - Unclear risk of bias - inadequate information to allow judgement of a study to be classified as 'low risk' or 'high risk'
  - High risk of bias - incomplete reporting of specified outcomes. One or more primary outcomes are reported using measurements or analysis that was not pre-specified. One or more of the primary outcomes was not pre-specified. One or more outcomes of interest were reported incompletely and could not be entered into meta-analysis. Results for a key outcome expected to be reported were excluded
- Size of study (checking for biases confounded by small size)
  - Low risk of bias ≥ 200 participants per treatment arm
  - Unclear risk of bias - 50 to 199 participants per treatment arm

- High risk of bias < 50 participants per treatment arm

- Other sources of bias
  - We will consider other factors including whether studies were stopped early, there were differences between groups at baseline, the timing of outcome measurement, co-intervention comparability, and funding declarations

Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system

- High: we are very confident that the true effect lies close to that of the estimate of the effect
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

We will decrease the GRADE rating by one (- 1) or two (- 2) if we identify:

- Serious (- 1) or very serious (- 2) limitation to study quality
- Important inconsistency (- 1)
- Some (- 1) or major (- 2) uncertainty about directness
- Imprecise or sparse data (- 1)
- High probability of reporting bias (- 1)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	14
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify	N/A

		as such and list changes; otherwise, state plan for documenting important protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	14
Sponsor	#5b	Provide name for the review funder and / or sponsor	14
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	14
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-8
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9-10 supplementary material
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary material
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-13
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently,	10

		in duplicate), any processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-11
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12-13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	12
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12-13
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

BMJ Open

The Clinical Efficacy of Transcutaneous Electrical Nerve Stimulation (TENS) for Acute and Chronic Pain: A Protocol for a Meta-Analysis of Randomized Controlled Trials (RCTs)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029999.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Jul-2019
Complete List of Authors:	Johnson, Mark; Leeds Beckett University Faculty of Health and Social Sciences, Centre for Pain Research Jones, Gareth; Leeds Beckett University, School of Clinical and Applied Sciences Paley, Carole; Leeds Beckett University, School of Clinical and Applied Sciences; Airedale NHS Foundation Trust, Research & Development Wittkopf, Priscilla; Leeds Beckett University - City Campus, School of Clinical and Applied Sciences
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	Transcutaneous electrical nerve stimulation, Pain, Systematic review, Meta-analysis

Title

The Clinical Efficacy of Transcutaneous Electrical Nerve Stimulation (TENS) for Acute and Chronic Pain: A Protocol for a Meta-Analysis of Randomized Controlled Trials (RCTs)

Authors

Mark I. Johnson, PhD[1]

Gareth Jones, PhD[1]

Carole Paley, PhD[1,2]

Priscilla Wittkopf, PhD[1]

Affiliations

1. Centre for Pain Research, Clinical and Applied Sciences, Leeds Beckett University, Leeds, LS1 3HE, U.K.

2. Research & Development Dept. Airedale NHS Foundation Trust, Steeton, Keighley BD20 6TD

Address for correspondence

Professor Mark I. Johnson

Telephone: (UK) 0113 2832600, e-mail: m.johnson@leedsbeckett.ac.uk

Word count: 4427

ABSTRACT

Introduction: The aim of this systematic review with meta-analysis is to evaluate the clinical efficacy of TENS for any type of acute and chronic pain in adults.

Methods and analysis: We intend to search electronic databases (Cochrane Library, MEDLINE, Embase, CINAHL, PsycINFO, LILACS, PEDRO, Web of Science, AMED, SPORTDiscus) from inception to the present day to identify all randomised controlled trials (RCT) on the use of TENS in adults for any type of pain including acute pain, chronic pain, and cancer-related pain. We will screen the RCTs against eligibility criteria for inclusion in our review. Two reviewers will independently undertake RCT selection, data extraction, and risk of bias assessment. Primary outcomes will be: (i) participant-reported pain relief of 30% or greater expressed as frequency (dichotomous) data; and (ii) participant-reported pain intensity expressed as mean (continuous) data. We will conduct meta-analyses to determine risk ratio for dichotomous data, and mean difference or standardised mean difference for continuous data for TENS versus placebo TENS, no treatment or waiting list control, standard of care (including exercise), and other treatments. Subgroup analyses will include different pain conditions (e.g. acute versus chronic), TENS intensity, during versus after TENS, TENS as a sole treatment versus TENS in combination with other treatments, and TENS administered as a single dose versus repetitive dose.

Ethics and dissemination: This systematic review will not use data from individual participants, and the results will be disseminated in a peer-reviewed publication and presented at a conference.

Keywords: Transcutaneous electrical nerve stimulation, Pain, Systematic review, Meta-analysis

ARTICLE SUMMARY

Strengths and Limitations of this Systematic Review

- There has been a long-standing debate about the efficacy of TENS because systematic reviews for specific medical conditions have been inconclusive due to insufficient data.
- This protocol defines a systematic review with meta-analysis of randomised controlled clinical trials to evaluate the clinical efficacy and safety of TENS for any type of acute and chronic pain in adults.
- The main strength of this protocol is the assessment of TENS on pain associated with a variety of conditions and this will provide clinicians, policy makers, and patients with a source of information on the effects of TENS for any type of pain.
- The main concerns of this protocol are that the variety of types of pain and types of TENS interventions has potential for clinical and statistical heterogeneity.

- These concerns will be managed by conducting pre-planned sub-group analyses of specific medical conditions based on ICD-11 categories, and optimal TENS techniques.

Ethics and dissemination

This is a secondary analysis of published studies, therefore no ethics approval required. Planned dissemination channels include a peer-reviewed publication, international conference presentation, and public engagement events.

Prospero registration number CRD42019125054

INTRODUCTION

Pain is a major healthcare issue. Estimates of the prevalence of acute pain in adults suggest that it may be as high as 70.7% in accident and emergency departments and 50% in hospital in-patients, with up to 35% of patients reporting severe pain.[1] Estimates of the worldwide prevalence of chronic pain in the general adult population suggest it may affect up to 45% of people, with up to 15% reporting severe disabling pain.[2-6] Pain is financially expensive in terms of medical consultations, treatments and time lost from work, and socially expensive in terms of suffering and impaired quality of life.[7 8] Gaskin and Richard [7] estimated that annual costs related to health care and loss of worker productivity in the United States was between $560 and $635 billion dollars. This was greater than heart disease ($309 billion), cancer ($243 billion), and diabetes ($188 billion). In Europe, Breivik, et al. [9] estimated the national healthcare and socioeconomic costs of chronic pain to be 3-10% of gross domestic product.

Approximately 40% of people living with chronic pain report inadequate pain management and over 60% report that medication does not adequately control pain.[10] Desirable pain-management strategies adopt a biopsychosocial approach using pharmacological and non-pharmacological interventions tailored to the individual. The goal of treatment is to relieve pain and improve physiological functioning associated with activities of daily living, role functioning associated with jobs and hobbies, and emotional, cognitive and social functioning associated with quality of life. Early pain management is critical to reduce the likelihood of acute pain developing into chronic pain. Transcutaneous electrical nerve stimulation (TENS) has been used across the world for the management of acute and chronic pain irrespective of cause, including pain related to cancer and its treatment.[11]

Description of the intervention

TENS is the delivery of pulsed electrical currents across the intact surface of the skin to stimulate peripheral nerves, principally for pain relief.[11] TENS may be self-administered by the patient, ideally following instruction from a healthcare practitioner using a portable, battery-powered TENS device to produce electrical currents that are delivered to the body using self-adhesive electrodes attached to the surface of the skin. TENS is available without prescription, is inexpensive and has a good safety profile compared with medication.[11] Contraindications include patients who also have cardiac pacemakers and implantable cardioverter defibrillators. Precautions include pregnancy, epilepsy, active malignancy, deep-vein thrombosis, and frail or damaged skin.[12 13] Two techniques are commonly used: conventional TENS administered to produce a strong non-painful TENS sensation at

the site of pain and acupuncture-like TENS to produce strong non-painful pulsate sensations, often accompanied by muscle twitching.[11] Evidence suggests that currents with pulse amplitudes (mA) that generate a strong, non-painful TENS sensation are critical for response and therefore pulse amplitude should be titrated during treatment to maintain this intensity level.[14-16] There has been a long-standing debate about the efficacy of TENS. Some clinical guidelines recommend TENS as an adjunct to core treatment whereas others do not (for review see[12 17]).

How the intervention might work

In 1965, Melzack and Wall [18] proposed that TENS could stimulate the low-threshold cutaneous afferents to inhibit onward transmission of nociceptive information in the central nervous system and thus, alleviate pain (i.e. segmental modulation[19 20]). In addition, TENS could stimulate small diameter muscle afferents to activate descending pain inhibitory pathways[21-23] or block afferent activity in peripheral neurons, creating a 'busy-line' effect.[24]

Previous Reviews

There is a plethora of systematic reviews on TENS for specific conditions and most are inconclusive (for review see[17 25]) An overview of Cochrane reviews provides tentative evidence that TENS reduces pain intensity when administered as a stand-alone treatment for acute pain in adults.[26] A meta-analysis found superiority of TENS over placebo for reducing postoperative analgesic consumption when administered using a strong, subnoxious intensity and adequate frequency.[14] A Cochrane review to assess the effects of TENS on pain in labour found limited evidence of effect but concluded women should have the choice of using it during childbirth.[27]

In 2008, a Cochrane review on TENS for chronic pain was inconclusive[28] although this review has now been withdrawn. An overview of Cochrane reviews on TENS for chronic pain included a descriptive analysis of nine reviews and 51 RCTs but did not pool data for meta-analyses .[29] It was not possible to conclude whether TENS was beneficial or harmful.[29] Most Cochrane reviews on specific chronic pain conditions are inconclusive (e.g. osteoarthritis of the knee [30], neuropathic pain[31], chronic low back pain[32], cancer pain[33], and phantom pain and stump pain[34]). Interestingly, non-Cochrane reviews with meta-analyses have found superiority of TENS over placebo for chronic musculoskeletal pain[35] and osteoarthritis of the knee.[36]

Systematic reviews and meta-analyses are hindered by methodological weaknesses of included RCTs. Bennett, et al.[37] harvested RCTs from Cochrane reviews on TENS for acute pain, chronic pain

and cancer-related pain and found that inadequate method of randomisation, small sample sizes, and issues associated with the implementation of a sham (placebo) control such as allocation concealment and blinding contributed to an overestimation of TENS effects. The design of an authentic placebo control is a challenge. Credible sham TENS devices have been used that are identical in appearance to real TENS devices and deliver no current or deliver stimulation at the start of treatment and fade to zero current output over a brief period of time (e.g. within 45 seconds).[38] It is not possible to blind participants to TENS sensation. Nevertheless, uncertainty about allocation to active and inactive TENS can be achieved by informing participants that some types of electrical stimulation devices do not produce sensation during stimulation (i.e. microcurrent therapy). Blinding can be monitored by asking participants whether they believed that '...the device was functioning properly?'.[39] Bennett, et al.[37] also found that aspects of fidelity may contribute to underestimation of TENS effects including inadequacy of TENS technique; inadequate dosing; and the effect of concurrent analgesia in placebo groups.[37]

Why it is important to do this review

Debate about the clinical efficacy of TENS for the relief of pain in adults has been ongoing since TENS was introduced in the early 1970s. The majority of systematic reviews published to date have been inconclusive, despite a vast number of published RCTs. This has resulted in contradictory recommendations from clinical guideline panels. For example, the National Institute of Health Care Excellence (NICE) recommend that TENS should be offered as an adjunct to core treatment for osteoarthritis[40] but not for non-specific chronic low back pain.[41]

Previous systematic reviews tend to focus on pain associated with specific medical conditions, in line with classical pathology-based categorisation based on pain as a secondary outcome of disease. This markedly reduces sample sizes of pooled data and the statistical power of the meta-analysis. In general, the findings of systematic reviews of the efficacy of TENS for specific medical conditions are inconclusive due to insufficient data. Methodological factors influencing estimates of efficacy include analyses used to measure treatment outcome, trial duration, withdrawals, and statistical imputation following withdrawal. Based on the work of Moore, et al. [42], the Pain, Palliative and Supportive Care group from Cochrane Collaboration suggest that trial arms with fewer than 200 participants in RCTs or fewer than 500 participants in meta-analyses are at a high risk of bias seriously undermining confidence in findings. To date, only two meta-analyses on TENS have come close to this threshold of acceptability and both found superiority over placebo (for acute post-operative pain[14] and chronic musculoskeletal pain[35]). Pooling data on pain intensity from RCTs irrespective of diagnostic condition

would markedly improve the statistical power associated with meta-analyses of TENS. However, inclusion of a wide variety of types of pain has potential for increasing heterogeneity. The recent overview of Cochrane reviews on TENS for chronic pain published by the Cochrane collaboration did not pool data and was inconclusive.[29]

The mechanism of action of TENS primarily involves neuromodulation of central nociceptive transmission irrespective of medical diagnosis. Therefore, TENS is used for symptomatic relief of pain rather than treatment (cure) of pathology. The relationship between pain experience, response to treatment and pathology is variable within and between individuals with similar conditions. Pain experience is complex and influenced by contextual, social, psychological and biological factors. Traditionally, pain is evaluated from a pathology-based perspective, and dichotomised into acute and chronic. Even when pain is attributed to a medical condition, the specifics of pathology driving an individual's pain may be illusive. Sometimes pain does not fit into a classical pathology-based category, as recognised by the World Health Organization who introduced a new phenomenological definition for chronic primary pain in the International statistical classification of diseases and related health problems (11th Revision, ICD-11).[43] Moreover, pathophysiological processes do not dichotomize at specific time points, leading Loeser to suggest that the dichotomy of pain into acute and chronic should be abolished.[44]

There has been no convincing evidence that TENS outcome is affected by the nature of pathology, the type of pain, or medical diagnoses.[11 45] Thus, it seems logical to undertake a meta-analysis of the clinical efficacy of TENS by evaluating pain outcomes from a phenomenological perspective, irrespective of medical condition. This would increase statistical power and confidence in findings, and provide clinicians, policy makers, and patients with a source of information on the effects of TENS for any type of pain. We appreciate that there may be substantial differences in the context in which different types of pain are experienced (e.g. acute versus chronic, negligible consequence versus life-threatening etc.) and that this has potential to generate clinical and statistical heterogeneity. Thus, concerns over an increase in clinical heterogeneity associated with combining different clinical conditions will be offset by conducting sub-group analyses of specific medical conditions based on ICD-11 categories if sufficient data is available.

Aim

The aim of this systematic review with meta-analysis is to evaluate the clinical efficacy and safety of TENS for any type of acute and chronic pain in adults. The review protocol has been adapted from a Cochrane review on TENS for fibromyalgia previously published by the investigators.[46]

METHODS

The protocol is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines. The completed checklist can be found in online supplementary material (Table S1).

Patient and Public Involvement

There is no direct patient or public involvement in this study. Patients were not involved in the development of the research question and outcome measures or the design of the systematic review. Patients will not be involved with the conduct of the systematic review.

Criteria for considering studies for this review

Types of studies

We plan to include randomised controlled trials (RCTs) of TENS treatment for acute or chronic pain of any origin. We will exclude studies that were non-randomised, case reports and clinical observations. We plan to include parallel group and crossover trial designs. We plan to include single treatment interventions without follow-up. However, we will conduct a subgroup analysis of RCTs that delivered at least two weeks of treatment and had a duration of at least eight weeks as these are considered as best practice. We require full journal publication of a full trial report. We will not include, online clinical trial results, summaries of otherwise unpublished clinical trials, abstracts or letters.

Types of participants

We will include RCTs of adult participants aged 18 years or above with any type of clinical pain.

Types of TENS interventions

We will include all RCTs that administered TENS as non-invasive electrical stimulation of the skin with the intention of exciting peripheral nerves to alleviate pain using a standard TENS device.[11]

Non-invasive

We will only include RCTs that administered TENS across the intact surface of the skin using surface electrodes. We will exclude invasive nerve stimulation techniques such as percutaneous electrical nerve stimulation and electro-acupuncture.

Type of TENS Device

We will only include RCTs that administered TENS using a standard TENS device,[11] regardless of the device manufacturer, that delivered biphasic or monophasic pulsed electrical currents. We will exclude RCTs that administered 'TENS-like' currents that are not typical output specifications of a standard TENS device.[11] We will exclude neuromuscular electrical stimulation (NMES) devices, interferential current devices, and microcurrent devices.[11] We will exclude TENS delivered using single probe electrodes (i.e. TENS pens) or using matrix electrodes and electrode arrays.

TENS Technique

We will include RCTs that used a standard TENS device irrespective of the term to describe the type of TENS technique (e.g. conventional TENS, acupuncture-Like TENS, high-frequency-low-intensity, low-frequency-high intensity, etc.). We will exclude RCTs that did not use pulsed electrical currents. We will only include RCTs that administered TENS on areas of the body that were sensate, and where electrodes were located at (a) the site of pain or (b) over nerve bundles proximal (or near) to the site of pain. We will include TENS delivered at acupuncture points only if the point was lying over nerve bundles proximal (or near) to the site of pain. We will include all RCTs irrespective of the current amplitude of TENS and/or participant-reported TENS intensity. We consider participant-reported strong but comfortable TENS sensations as optimal and will conduct a subgroup analysis to compare TENS at intensities described as 'strong' (optimal) versus those described as 'mild', 'faint', or 'barely perceptible' (sub-optimal). We will include RCTs that delivered TENS at intensities reported to generate muscle twitches providing TENS was administered using a standard TENS device with the primary goal to alleviate pain. We will only include RCTs that delivered pulse frequencies of TENS that were less than 250 pulses per second and pulse durations less than 1 millisecond. We will include any type of pulse pattern.

Dosage and Regimen

We will include RCTs that administered TENS for any duration or regularity of treatment. We will include TENS that was administered by a therapist and/or self-administered by study participants.

Evaluation of TENS Treatment Effects

We will include TENS administered as a sole treatment or in combination with usual care and/or other treatments. We will exclude RCTs where it was not possible to isolate the effects of TENS from other treatments. We will include RCTs that evaluate TENS versus:

- placebo TENS (e.g. sham (no current) TENS device);
- no treatment or waiting list control;
- standard of care (including exercise); and
- another treatment, both pharmacological and non-pharmacological.

We will include two TENS interventions from the same RCT. To avoid 'double-counting' and unit-of-analysis errors we will not enter several interventions versus one comparison group in common (e.g. placebo TENS) into the same meta-analysis. We will follow recommendations from Cochrane to combine TENS intervention groups to create a single pairwise comparison unless one or more of the TENS interventions do not meet our criteria for optimal TENS technique as described in the section TENS Technique. In such situations, we will select one TENS intervention that meets the criteria for optimal technique.

Criteria and Credibility of Placebo TENS

The credibility and blinding of placebo TENS is an issue in TENS studies as it is not possible to blind participants to TENS sensation, although it is possible to generate uncertainty about allocation to active and inactive TENS.[39] We define a sham TENS device as a device similar in appearance to the real TENS device used in the study but where the current output was modified so that there is no electrical current, or a barely perceptible electrical current and/or electrical current that ceases within one minute.[16 38] We will identify RCTs that attempt to assess the credibility of placebo TENS and will conduct a subgroup analysis of RCTs that judge the intervention to be a credible placebo TENS.

Search methods for identification of studies

The systematic review process will be guided by the Cochrane Collaboration of Systematic Reviews[47] and the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.[48] We will conduct a literature search to identify RCTs published from date of inception of the database (Supplementary material - Appendix 1) and screen them against our eligibility criteria for inclusion in our review. The purpose of the search is to provide comprehensive coverage of a wide variety of pain conditions (e.g. ICD-11 categories) at various stages and settings (e.g. acute, chronic, palliative, community, primary, secondary, tertiary). Also, we will conduct a literature search to identify systematic reviews published from inception and will harvest RCTs to gain insights to the consistency

of RCTs included across systematic reviews of similar conditions, including our own (Supplementary material Appendix 2). There is no intention to evaluate or quality assess previously published systematic reviews.

Electronic searches

We will search the following electronic databases using a combination of controlled vocabulary, i.e. medical subject headings (MeSH) and free-text terms to identify published RCTs and systematic reviews from inception to the date of the search.

- Cochrane Library (CENTRAL);
- MEDLINE (via PubMed);
- Embase (via OVID);
- CINAHL (via EBSCO);
- PsycINFO (via EBSCO);
- LILACS (via Birme);
- PEDRO;
- Web of Science;
- AMED (via OVID);
- SPORTDiscus (via EBSCO).

We will tailor searches to the individual databases by adapting the MEDLINE search strategy for the other databases listed. There will be no language restrictions and we will identify all relevant RCTs irrespective of language and will translate articles where required.

Data collection and analysis

Selection of studies

Two review authors will independently screen records to identify RCTs. We will remove duplicates and eliminate records that clearly do not satisfy the inclusion criteria. Full text reports of potentially eligible RCTs will be obtained and screened for eligibility by two review authors. Also, two review authors will screen records to identify systematic reviews on TENS and will read full text reports to create a list of RCTs included in each systematic review. Disagreements at any stage of the process will be resolved by consensus using a third review author as arbiter. We will not anonymise records of systematic reviews or RCTs in any way before assessment. We will create a PRISMA flow chart.[47 48]

Data extraction and management

Two review authors will extract data from included RCTs independently and will check for agreement before entry into a software. Disagreement will be resolved by consensus with a third author acting as arbiter. We will include information about study design, study participants, sample size, and interventions used. We will use this data to populate a 'Characteristics of included RCTs' table (supplementary material Appendix 3). We will contact authors via email to clarify issues relating to inclusion, risk of bias and missing data.

Types of outcome measures

We will include RCTs that measure pain using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We will include measures of pain at rest and pain on movement. We will extract pain measures assessed using condition specific questionnaires (e.g. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Fibromyalgia Impact Questionnaire (FIQ)). We plan to extract outcome measurement data before, during, and after the intervention, where data is available. We plan to extract data on clinical status or health-related quality of life and treatment satisfaction. We will capture data for adverse effects of any type or severity as descriptions from participants and number of withdrawals and/or stopping of treatment. Serious adverse events are defined as untoward medical occurrence or effect resulting in death, threat to life, hospitalisation, significant disability or incapacity, congenital anomaly or birth defect.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[47] Risk of bias assessment consists of assessment of selection bias, attrition bias, blinding and sample size (supplementary material Appendix 4).

Measures of treatment effect

Pain outcomes tend to have a U-shaped distribution with some patients experiencing substantial reductions in pain and others experiencing minimal or no improvement.[49] Thus, data expressed as averages may be misleading as a small average between-group effect size may represent a proportion of participants that actually responded very well to the intervention.[50] We do not know whether outcomes are bi-modally distributed in trials of TENS but we expect most RCTs in this review to present effect sizes as the average between intervention groups. There is little consensus or evidence regarding what the threshold should be for a clinically important difference in pain

intensity based on the between-group difference during or after the intervention. The Outcome Measures in Rheumatology (OMERACT 12)[51] group states that the proportion of patients achieving one or more thresholds of improvement from baseline pain should be reported in addition to mean change. We will follow the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions when analysing response to treatment and consider reports of pain relief of 30% or greater compared to baseline as responders.[52]

Primary outcomes

Proportion of participant-reported pain relief of ≥30% expressed as frequency (dichotomous) data

Our primary outcome is responder rate. The proportion of participants reporting pain relief of 30% or greater (i.e. at least moderate pain relief) compared with baseline in each group will be classed as responders.[49 53] We will calculate risk ratio (RR) and risk difference (RD) with 95% confidence intervals (CI). Comparisons between groups will then be finalised by calculating the number needed to treat to benefit (NNTB) as an absolute measure of treatment effect where possible.[52]

Participant-reported pain intensity expressed as mean (continuous) data

We intend to calculate mean difference (MD) with 95% CI for continuous data collected on identical scales. We intend to calculate standardised mean difference (SMD) with 95% CI for continuous data collected on different scales. We intend to use a between-group difference of ≥10 mm on a 0 to 100 mm VAS for minimally important outcome for pain intensity. We will interpret these findings with caution as it remains possible that estimates that fall close to this point may reflect a treatment that benefits an appreciable number of patients. In addition, we will calculate the difference between groups in the percentage change in pain intensity during treatment relative to baseline. This will enable us to classify according to IMMPACT criteria for clinically important change, as previously used in Cochrane reviews, where no important change < 15%, minimally important change 15% > 30%, moderately important change 30% > 50% and substantially important change ≥ 50%.[52]

Secondary outcomes

- Proportion of participants reporting pain relief of 50% or greater (i.e. at least substantial pain relief).
- Participant-reported condition-specific pain-related outcomes (e.g. WOMAC, FIQ).
- Participant-reported clinical status or health-related quality of life, including activities of daily living and fatigue, using any validated tool (e.g. Patient Global Impression of Change (PGIC), Short Form Health Survey (SF-36), EuroQol instruments).

- Participant-reported treatment satisfaction.
- Participant-reported adverse events expressed as frequency (dichotomous) data and/or severity.

Dichotomous and continuous data will be analysed using the same procedures described for primary outcomes. For health-related quality of life data, we intend to consider a difference greater than 10% of the scale employed to be minimally important.[54]

Unit of analysis issues

We will include cross-over designs but intend only to enter the first period data into the meta-analysis. If this was not reported, we will note this and not include the data. If data is reported appropriately then we intend to include the data using the generic inverse variance feature.

Dealing with missing data

An intention-to-treat (ITT) analysis will be used when the ITT population were randomised, received at least one dose of TENS, and provided at least one post-baseline outcome measurement. Missing participants will be assigned zero improvement wherever possible.

Assessment of heterogeneity

We will examine heterogeneity using visual inspection of forest plots, L'Abbé Plots [55], the I^2 statistic and the Chi^2 test, if appropriate.[56] We will use the Cochrane Collaboration's rough guide to interpretation as not important (0% to 40%), moderate (30% to 60%), substantial (50% to 90%) and considerable (75% to 100%). We will use a random effects model since the studies are anticipated to be heterogeneous. This accounts for heterogeneity among study results beyond the variation associated with fixed-effects model. Sources of heterogeneity will be investigated with sub group analysis and/or a random-effects meta-regression analysis. We anticipate that causes of heterogeneity may be: clinical condition, acute vs chronic pain, and optimal vs suboptimal TENS. All analyses will be conducted contingent on data availability.[57]

Assessment of reporting biases

Publication bias will be assessed using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean a NNTB of 10[58]). The influence of small study samples will be assessed using the risk of bias criterion "study size". We plan to visually inspect funnel plots to explore the likelihood of reporting biases if there are

at least 10 RCTs in a meta-analysis and if RCTs differed in sample size. We will use Egger's test to detect small study bias for RCTs using continuous outcomes.[47]

Data synthesis

We will pool data using Review Manager[59] and will undertake meta-analyses of outcome data using a random-effects model. We will group data according to outcome and measurement time points as: (i) during stimulation or immediately after stimulation at each treatment session, or both; and (ii) post-intervention follow-up at less than two weeks post-intervention (short-term), two to seven weeks post-intervention (mid-term), and eight weeks or more post-intervention (long-term).

We plan to undertake a narrative synthesis if data is inadequate to support statistical pooling.

Quality of the Evidence

We consider single RCTs too imprecise, unless the sample size is greater than 400 participants for continuous data and greater than 300 events for dichotomous data. We will present the outcome of the 'Risk of Bias' assessments in the reporting. We consider pooled data to be imprecise unless the sample size for a treatment arm is greater than 500 participants. We will present pooled effects for outcomes with GRADE judgements in 'Summary of findings' tables. Two review authors will independently rate the quality of outcomes using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system (GRADEpro GDT 2015, supplementary material Appendix 5).

Subgroup analysis

We plan to undertake subgroup analyses for acute versus chronic pain and for specific painful conditions. We also plan to conduct subgroup analyses to investigate the possible impact of TENS technique on analgesic efficacy as follows:

- Optimal intensity described as 'strong' versus sub-optimal intensity described as 'barely perceptible', 'faint', or 'mild';
- Conventional TENS versus acupuncture-like TENS;
- Assessment during TENS versus after TENS;
- TENS administered as a sole treatment versus TENS administered in combination with other treatments; and
- TENS administered as a single dose versus repetitive dose.

Post subgroup analysis we contemplate conducting a network meta-analysis contingent on meeting transitivity assumption.

Sensitivity analysis

We plan to analyse the effect of excluding RCTs with high risk of bias.

Ethics and dissemination

This systematic review will not use data from individual participants to protect privacy, and the results will be disseminated in a peer-reviewed publication and presented at a scientific conference.

Funding

The review is funded by an Investigator Sponsored Study grant from GlaxoSmithKline. No external assistance was provided for the design, delivery or writing of this review.

Competing interests

Mark I. Johnson's institution has received research and consultancy funding for work that he has undertaken for GlaxoSmithKline.

Acknowledgements

None

Accessing research materials

Underlying materials related to this protocol and subsequent review can be accessed by contacting Professor Mark I. Johnson.

Author contributions

MIJ conceived the study.

MIJ and PGW created the first draft of the protocol which was then revised by GJ and CP.

The search strategy was developed by PGW.

All authors approved the publication of the protocol.

REFERENCES

1. Mura P, Serra E, Marinangeli F, et al. Prospective study on prevalence, intensity, type, and therapy of acute pain in a second-level urban emergency department. *J Pain Res* 2017;10:2781-88. doi: 10.2147/JPR.S137992

2. Elzahaf RA, Tashani OA, Unsworth BA, et al. The prevalence of chronic pain with an analysis of countries with a Human Development Index less than 0.9: a systematic review without meta-analysis. *Current medical research and opinion* 2012;28(7):1221-9. doi: 10.1185/03007995.2012.703132 [published Online First: 2012/06/16]
3. Jackson T, Thomas S, Stabile V, et al. A Systematic Review and Meta-Analysis of the Global Burden of Chronic Pain Without Clear Etiology in Low- and Middle-Income Countries: Trends in Heterogeneous Data and a Proposal for New Assessment Methods. *Anesth Analg* 2016;123(3):739-48. doi: 10.1213/ANE.0000000000001389
4. Fayaz A, Croft P, Langford RM, et al. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open* 2016;6(6):e010364. doi: 10.1136/bmjopen-2015-010364 [published Online First: 2016/06/22]
5. Macfarlane GJ. The epidemiology of chronic pain. *Pain* 2016;157(10):2158-9. doi: 10.1097/j.pain.0000000000000676
6. Gregory J, McGowan L. An examination of the prevalence of acute pain for hospitalised adult patients: a systematic review. *J Clin Nurs* 2016;25(5-6):583-98. doi: 10.1111/jocn.13094 [published Online First: 2016/01/19]
7. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012;13(8):715-24. doi: 10.1016/j.jpain.2012.03.009 [published Online First: 2012/05/23]
8. Goldberg D, McGee S. Pain as a global public health priority. *BMC Public Health* 2011;11(1):770.
9. Breivik H, Eisenberg E, O'Brien T. The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care. *BMC Public Health* 2013;13:1229-29. doi: 10.1186/1471-2458-13-1229
10. Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006;10(4):287-333. doi: 10.1016/j.ejpain.2005.06.009
11. Johnson M. Transcutaneous electrical nerve stimulation (TENS). Research to support clinical practice. Oxford, UK: Oxford University Press 2014.
12. Johnson MI, Bjordal JM. Transcutaneous electrical nerve stimulation for the management of painful conditions: focus on neuropathic pain. *Expert review of neurotherapeutics* 2011;11(5):735-53. doi: 10.1586/ern.11.48 [published Online First: 2011/05/05]
13. Houghton P, Nussbaum E, Hoens A. Electrophysical agents. Contraindications and Precautions: An Evidence-Based Approach to Clinical Decision Making in Physical Therapy. *Physiotherapy Canada* 2010;62(5):5-80.
14. Bjordal JM, Johnson MI, Ljunggreen AE. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. *Eur J Pain* 2003;7(2):181-8.
15. Moran F, Leonard T, Hawthorne S, et al. Hypoalgesia in response to transcutaneous electrical nerve stimulation (TENS) depends on stimulation intensity. *J Pain* 2011;12(8):929-35. doi: S1526-5900(11)00444-5 [pii] 10.1016/j.jpain.2011.02.352 [published Online First: 2011/04/13]
16. Sluka KA, Bjordal JM, Marchand S, et al. What Makes Transcutaneous Electrical Nerve Stimulation Work? Making Sense of the Mixed Results in the Clinical Literature. *Physical therapy* 2013;May 2. [Epub ahead of print] doi: ptj.20120281 [pii] 10.2522/ptj.20120281 [published Online First: 2013/05/04]
17. Johnson MI, Jones G. Transcutaneous electrical nerve stimulation: current status of evidence. *Pain Manag* 2017;7(1):1-4. doi: 10.2217/pmt-2016-0030
18. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150(3699):971-9. [published Online First: 1965/11/19]
19. Garrison DW, Foreman RD. Effects of transcutaneous electrical nerve stimulation (TENS) on spontaneous and noxiously evoked dorsal horn cell activity in cats with transected spinal cords. *Neuroscience Letters* 1996;216(2):125-8.

20. Ma YT, Sluka KA. Reduction in inflammation-induced sensitization of dorsal horn neurons by transcutaneous electrical nerve stimulation in anesthetized rats. *Experimental Brain Research* 2001;137(1):94-102.
21. Desantana JM, da Silva LF, de Resende MA, et al. Transcutaneous electrical nerve stimulation at both high and low frequencies activates ventrolateral periaqueductal grey to decrease mechanical hyperalgesia in arthritic rats. *Neuroscience* 2009
22. Francis RP, Johnson MI. The characteristics of acupuncture-like transcutaneous electrical nerve stimulation (acupuncture-like TENS): a literature review. *Acupuncture and Electro-Therapeutics Research* 2011;36(3-4):231-58. [published Online First: 2011/01/01]
23. Kalra A, Urban MO, Sluka KA. Blockade of opioid receptors in rostral ventral medulla prevents antihyperalgesia produced by transcutaneous electrical nerve stimulation (TENS). *The Journal of pharmacology and experimental therapeutics* 2001;298(1):257-63.
24. Nardone A, Schieppati M. Influences of transcutaneous electrical stimulation of cutaneous and mixed nerves on subcortical and cortical somatosensory evoked potentials. *Electroencephalogr Clin Neurophysiol* 1989;74(1):24-35.
25. Johnson MI. Transcutaneous electrical nerve stimulation (TENS) as an adjunct for pain management in perioperative settings: a critical review. *Expert review of neurotherapeutics* 2017;17(10):1013-27. doi: 10.1080/14737175.2017.1364158
26. Johnson MI, Paley CA, Howe TE, et al. Transcutaneous electrical nerve stimulation for acute pain. *Cochrane Database Syst Rev* 2015;6:CD006142. doi: 10.1002/14651858.CD006142.pub3 [published Online First: 2015/06/16]
27. Dowswell T, Bedwell C, Lavender T, et al. Transcutaneous electrical nerve stimulation (TENS) for pain relief in labour. *Cochrane Database Syst Rev* 2009(2):CD007214.
28. Nnoaham KE, Kumbang J. Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Database Syst Rev* 2008(3):CD003222.
29. Gibson W, Wand BM, Meads C, et al. Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2019(2) doi: 10.1002/14651858.CD011890.pub2
30. Rutjes AW, Nuesch E, Sterchi R, et al. Transcutaneous electrostimulation for osteoarthritis of the knee. *Cochrane Database Syst Rev* 2009(4):CD002823.
31. Gibson W, Wand BM, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults. *Cochrane Database Syst Rev* 2017;9:CD011976. doi: 10.1002/14651858.CD011976.pub2
32. Khadilkar A, Odebiyi DO, Brosseau L, et al. Transcutaneous electrical nerve stimulation (TENS) versus placebo for chronic low-back pain. *Cochrane Database Syst Rev* 2008(4):CD003008.
33. Hurlow A, Bennett MI, Robb KA, et al. Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. *Cochrane Database Syst Rev* 2012;3:CD006276. doi: 10.1002/14651858.CD006276.pub3 [published Online First: 2012/03/16]
34. Johnson MI, Mulvey MR, Bagnall AM. Transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain following amputation in adults. *Cochrane Database Syst Rev* 2015;8:CD007264. doi: 10.1002/14651858.CD007264.pub3 [published Online First: 2015/08/19]
35. Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: a meta-analysis of randomized controlled trials. *Pain* 2007;130(1-2):157-65.
36. Bjordal JM, Johnson MI, Lopes-Martins RA, et al. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials. *BMC musculoskeletal disorders* 2007;8:51.
37. Bennett MI, Hughes N, Johnson MI. Methodological quality in randomised controlled trials of transcutaneous electric nerve stimulation for pain: low fidelity may explain negative findings. *Pain* 2011;152(6):1226-32. doi: 10.1016/j.pain.2010.12.009 [published Online First: 2011/03/26]

38. Rakel B, Cooper N, Adams HJ, et al. A new transient sham TENS device allows for investigator blinding while delivering a true placebo treatment. *J Pain* 2010;11(3):230-8. doi: 10.1016/j.jpain.2009.07.007
39. Deyo RA, Walsh NE, Schoenfeld LS, et al. Can trials of physical treatments be blinded? The example of transcutaneous electrical nerve stimulation for chronic pain. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists* 1990;69(1):6-10.
40. National Institute for Health and Care Excellence. Osteoarthritis: care and management. NICE guidelines [CG177] London, 2014:1-37.
41. National Institute for Health and Care Excellence. Low back pain and sciatica in over 16s: assessment and management. Clinical guideline [NG59]: National Institute for Health and Care Excellence (NICE), 2016:1-18.
42. Moore RA, Gavaghan D, Tramer MR, et al. Size is everything--large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;78(3):209-16. [published Online First: 1998/12/31]
43. WHO. International statistical classification of diseases and related health problems (11th Revision): World Health Organization, 2018.
44. Loeser JD. A new way of thinking about pain. *Pain Manag* 2018 doi: 10.2217/pmt-2018-0061
45. Johnson MI, Ashton CH, Thompson JW. An in-depth study of long-term users of transcutaneous electrical nerve stimulation (TENS). Implications for clinical use of TENS. *Pain* 1991;44(3):221-9.
46. Johnson MI, Claydon LS, Herbison GP, et al. Transcutaneous electrical nerve stimulation (TENS) for fibromyalgia in adults. *Cochrane Database Syst Rev* 2017;10:CD012172. doi: 10.1002/14651858.CD012172.pub2
47. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0 [Updated March 2011], 2011.
48. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews* 2015;4(1):1.
49. Moore RA, Moore OA, Derry S, et al. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. *Annals of the Rheumatic Diseases* 2010;69(2):374-9. doi: 10.1136/ard.2009.107805 ard.2009.107805 [pii] [published Online First: 2009/04/15]
50. Moore RA, Derry S, Wiffen PJ. Challenges in design and interpretation of chronic pain trials. *British journal of anaesthesia* 2013;111(1):38-45. doi: 10.1093/bja/aet126
51. Busse JW, Bartlett SJ, Dougados M, et al. Optimal Strategies for Reporting Pain in Clinical Trials and Systematic Reviews: Recommendations from an OMERACT 12 Workshop. *J Rheumatol* 2015 doi: 10.3899/jrheum.141440
52. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9(2):105-21.
53. Moore A, Derry S, Eccleston C, et al. Expect analgesic failure; pursue analgesic success. 2013;346:f2690. doi: 10.1136/bmj.f2690 %J BMJ : British Medical Journal
54. Furlan AD, Malmivaara A, Chou R, et al. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015;40(21):1660-73. doi: 10.1097/brs.0000000000001061 [published Online First: 2015/07/25]
55. L'ABBÉ KA, Detsky AS, O'rourke K. Meta-analysis in clinical research. *Annals of internal medicine* 1987;107(2):224-33.
56. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557
57. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002;21(11):1559-73. doi: 10.1002/sim.1187 [published Online First: 2002/07/12]

58. Moore RAB, J.; Derry, S.; McQuay, H.J. Managing potential publication bias. In: McQuay HJ KE, Moore RA, ed. Systematic Reviews in Pain Research: Methodology Refined. Seattle: IASP Press 2008:15-25.
59. Review Manager (RevMan) [program]. 5.3 version. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Supplementary material

Appendix 1 - MEDLINE Search Strategy for RCTs:

1. EXP Transcutaneous Electric Nerve Stimulation/

2 TENS.ti,ab

3 TNS.ti,ab

4 ENS.ti,ab

5 transcutaneous electric* nerve stimulation.ti,ab.

6 transcutaneous nerve stimulation.ti,ab

7 electric* nerve stimulation.ti,ab

8 electrostimulation therap*.ti,ab

9 electro-stimulation therap*.ti,ab.

10 electric* nerve therap*.ti,ab

11 electroanalgesi*.ti,ab

12 transcutaneous electric* stimulation.ti,ab.

13 TES.ti,ab

14 or/1-13

15 Pain

16 Randomized controlled trial. pt.

17 Controlled clinical trial.pt.

18 16 OR 17

19 14 AND 15 AND 18

Appendix 2 - MEDLINE Search Strategy for systematic reviews:

1. EXP Transcutaneous Electric Nerve Stimulation/

2 TENS.ti,ab

3 TNS.ti,ab

4 ENS.ti,ab

5 transcutaneous electric* nerve stimulation.ti,ab.

6 transcutaneous nerve stimulation.ti,ab

7 electric* nerve stimulation.ti,ab

8 electrostimulation therap*.ti,ab

9 electro-stimulation therap*.ti,ab.

10 electric* nerve therap*.ti,ab

11 electroanalgesi*.ti,ab

12 transcutaneous electric* stimulation.ti,ab.

13 TES.ti,ab

14 or/1-13

15 Pain

16 Systematic review. Pt.

17 Meta-analysis.pt.

18 16 OR 17

19 14 AND 15 AND 18

Appendix 3 - Data extraction

- Study Design
  - Cross-over, parallel-group,
  - Setting
  - Study duration
  - Methods of sequence generation and allocation concealment, blinding, intention-to-treat or per protocol analysis
- Study Participants
  - Age, gender
  - Pain diagnosis, duration of pain and symptoms
- Sample size
  - Active and comparator groups
- Interventions used
  - TENS
    - Type of TENS device (e.g. standard or 'TENS-like')
    - Electrode placement
    - Electrical characteristics of TENS (pulse frequency, waveform, amplitude/intensity, duration)
    - Dosage (treatment time and frequency)
    - Setting (where TENS was applied and by whom)
    - Adverse effects
  - Comparison group(s)
    - Type
    - Method of delivery (e.g. if placebo TENS then details of electrode placement, characteristics of placebo TENS (pulse frequency, waveform, amplitude/intensity, duration)
    - Dosage (treatment time and frequency)
    - Setting (where it was applied and by whom)
    - Adverse effects
  - Concomitant treatments
    - Pharmacological and non-pharmacological
  - Outcomes
    - Type
    - Time points used including follow-up

- Withdrawals
- Adverse and serious adverse effects
- Other

Sponsorship, country of origin, conflict of interest statements.

Appendix 4 - Assessment of risk of bias in included studies

- Random allocation sequence generation (checking for possible selection bias)
    - Low risk of bias - any truly random process, e.g. random number table; computer random number generator
    - Unclear risk of bias - method used to generate sequence not clearly stated
    - We will exclude studies using a non-random process such as odd or even date of birth; hospital or clinic record number
- Allocation concealment (checking for possible selection bias)
    - Low risk of bias - e.g. telephone or central randomization; consecutively numbered, sealed, opaque envelopes
    - Unclear risk of bias - method not clearly stated
    - High risk of bias - studies that do not conceal allocation (e.g. open list)
- Blinding of outcome assessment (checking for possible detection bias)
    - Blinding of participants
        - Low risk of bias - participants blinded to allocated intervention and unlikely that blinding broken
        - Unclear risk of bias - insufficient information to permit judgement of low/high risk of bias
        - High risk of bias - participants not blinded to allocated intervention OR participants blinded to allocated intervention but it was likely that blinding may have been broken
    - Blinding of care provider
        - Low risk of bias - care provider blinded to allocated intervention and unlikely that blinding broken
        - Unclear risk of bias - insufficient information to permit judgement of low/high risk of bias
        - High risk of bias - care provider not blinded to allocated intervention and the two interventions clearly identifiable to the care provider as experimental and control OR care provider blinded to allocated intervention but likely that blinding was broken
    - Blinding of assessor
        - Low risk of bias - outcome assessor (including 'participants' with respect to self-report outcomes) blinded to participants' allocated intervention and unlikely that blinding broken

        - Unclear risk of bias - insufficient information to permit judgement of low/high risk of bias
        - High risk of bias - outcome assessor (including 'participants' with respect to self-report outcomes) un-blinded to participants' allocated intervention OR outcome assessor blinded to allocated intervention but likely that blinding was broken
- Incomplete outcome data (drop-outs)
    - Low risk of bias < 20% drop-out and appears to be random with numbers per group provided along with reasons for drop-out
    - Unclear risk of bias < 20% and unclear if random with numbers per group and reasons for drop-out not described
    - High risk of bias ≥ 20% drop-out
- Incomplete outcome data (protocol violations)
    - Low risk of bias - if participants were analyzed in the group to which they were originally assigned
    - Unclear risk of bias - where insufficient information is provided to determine if analysis was per protocol or intention-to-treat
    - High risk of bias - where per protocol analysis was used, where available data were not analyzed or participants' data were included in the group to which they were not originally assigned
- Selective reporting
    - Low risk of bias - study protocol was available and all pre-specified outcomes were reported or study protocol was not available but all expected outcomes were reported
    - Unclear risk of bias - inadequate information to allow judgement of a study to be classified as 'low risk' or 'high risk'
    - High risk of bias - incomplete reporting of specified outcomes. One or more primary outcomes are reported using measurements or analysis that was not pre-specified. One or more of the primary outcomes was not pre-specified. One or more outcomes of interest were reported incompletely and could not be entered into meta-analysis. Results for a key outcome expected to be reported were excluded
- Size of study (checking for biases confounded by small size)
    - Low risk of bias ≥ 200 participants per treatment arm
    - Unclear risk of bias - 50 to 199 participants per treatment arm

- High risk of bias < 50 participants per treatment arm

- Other sources of bias
  - We will consider other factors including whether studies were stopped early, there were differences between groups at baseline, the timing of outcome measurement, co-intervention comparability, and funding declarations

Appendix 5- Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system

- High: we are very confident that the true effect lies close to that of the estimate of the effect
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

We will decrease the GRADE rating by one (- 1) or two (- 2) if we identify:

- Serious (- 1) or very serious (- 2) limitation to study quality
- Important inconsistency (- 1)
- Some (- 1) or major (- 2) uncertainty about directness
- Imprecise or sparse data (- 1)
- High probability of reporting bias (- 1)

Table S1 - Reporting checklist for protocol of a systematic review.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	16
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	16
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10-11 supplementary material

Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary material
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-12
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12-13
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	13
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12/14
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	12
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12-14
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15-16
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14

Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	15

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify	N/A

		as such and list changes; otherwise, state plan for documenting important protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	16
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	16
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10-11 supplementary material
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary material
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-12
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently,	11

		in duplicate), any processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-11
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12-13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	13
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12/14
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15-16
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	15